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DNA methylation and histone modifications correlate with RNA stability

Amit Blumberg
Weizmann Institute of Science, Rehovot, Israel

Background: The concentrations of distinct types of RNA in cells result from a dynamic equilibrium between RNA synthesis and decay. Despite the critical importance of RNA decay rates, current approaches for measuring them are generally labor-intensive, limited in sensitivity, and/or disruptive to normal cellular processes. Here, we introduce a simple method for estimating relative RNA half-lives that is based on two standard and widely available high-throughput assays: Precision Run-On sequencing (PRO-seq) and RNA sequencing (RNA-seq).

Methods: Our method treats PRO-seq as a measure of transcription rate and RNA-seq as a measure of RNA concentration, and estimates the rate of RNA decay required for a steady-state equilibrium. We show that this approach can be used to assay relative RNA half-lives genome-wide, with good accuracy and sensitivity for both coding and noncoding transcription units. Using a structural equation model (SEM), we test several features of transcription units, nearby DNA sequences, and nearby epigenomic marks for associations with RNA stability after controlling for their effects on transcription. We find that RNA splicing-related features are positively correlated with RNA stability, whereas features related to miRNA binding and DNA methylation are negatively correlated with RNA stability. We also identify several histone modifications that are associated with RNA stability.

Conclusion: We introduce an approach for estimating the relative half-lives of individual RNAs. Together, our estimation method and systematic analysis shed light on the pervasive impacts of RNA stability on cellular RNA concentrations. Furthermore, our findings support substantial evidence for connections between events that occur before or during transcription and a variety of post-transcriptional processes, some of which impact RNA stability.

amit.blumberg@weizmann.ac.il